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Abstract

The hydration behavior of an amphiphilic excipient, Gelucire 44/14, has been investigated. Two types of hydration processes were studied: one with increasing humidity to investigate the conditions during storage, and one with increasing water contents to study the behavior during dissolution. In addition, the main components of the excipient were investigated separately. These were polyethylene glycol (PEG), PEG monolaurate and PEG dilaurate (PEG esters), trilaurin (glyceride) and glycerol. The water uptake of Gelucire 44/14 at humidity ratios less than 60%RH was very low (about 1 wt%), which was attributed to the dissolution of the most hydrophilic component, glycerol. The water uptake increased substantially above 70%RH as PEG started to dissolve, followed by the PEG esters. It was concluded that each component equilibrates separately with the aqueous solution, which itself is in equilibrium with the humid air. Hence, a liquid phase can form between the crystals with a chemical potential decided by the humidity ratio. The water uptake of Gelucire 44/14 could be described as a sum of the uptake of the individual components, weighted according to their relative amounts in the mixture. Phase maps of the Gelucire 44/14 and its components at different water contents were constructed. Dry Gelucire 44/14 contains lamellar crystals of mainly PEG and PEG esters which melt at 44 ºC. The crystals do not swell at increasing humidity, but dissolve above 75%RH at a water content of 5 wt% in the excipient. At increasing water contents Gelucire 44/14 forms white gels composed of hexagonal and lamellar mesophases dispersed in a continuous liquid phase. These liquid crystalline phases dissolve at 35 ºC, i.e. below physiological temperatures. A dramatic viscosity maximum was observed in the lamellar region at 50 wt% water, which may be attributed to the formation of networks of PEG esters. The pure PEG esters were found to form cubic mesophases at 50 wt% water. The instruments used in this study were Dynamic Vapor Sorption (DVS), Thermal Gravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC), Small- and Wide Angle X-ray Scattering (SWAXS) and Optical Microscopy.

Keywords

Gelucire 44/14; phase diagram; hydration; DVS; SWAX

1. Introduction

Gelucires are a group of amphiphilic excipients which have been widely studied as controlled release matrices (Mouricout et al., 1990). The incorporation of drugs into Gelucires has been reported to increase the dissolution rate of poorly soluble drugs, often leading to improved drug bioavailability (Gines et al., 1995; Damian et al., 2000; Perissutti et al., 2000; Gupta et al., 2001). One compound from this group is Gelucire 44/14. This amphiphilic excipient has a Hydrophilic-Lipophilic Balance of 14 and a melting temperature of 44 °C, hence its name (Roussin et al., 1997).

In pharmaceutical applications, it is important to know how the excipient interacts with the drug, and how the mixture behaves during manufacturing, storage as well as during administration. These behaviours depend on the effects of temperature and hydration on the physical state of the excipient. For instance, dissolution or dispersion of a drug in the excipient can be modified according to water content; conversely, the synthesized drug may be hydrated, and this water may alter the physical state of the excipient (Damian et al., 2002; Sutananta et al., 1994a; Jeanmaire-Wolf et al., 1990). The excipient-drug mixture may then be stored at a certain relative humidity, and moisture form the air may have an effect on its physical state. Finally, during administration, the mixture will be immersed in body fluids, and it is important to know what are the pathways for dissolution in this aqueous medium.

There have been a few studies of the thermal behaviour of dry Gelucires (Craig et al., 1991; Sutananta et al., 1994b), but, to our knowledge, no systematic study of their hydration behaviour. The aim of this project was to investigate the behaviour of the Gelucire 44/14 when exposed to humidity and water, at ambient and physiological temperatures. We studied two hydration processes, corresponding respectively to the conditions encountered during storage and during dissolution of excipients. *During storage*, the excipients may be kept in equilibrium with an atmosphere of constant relative humidity (RH). Accordingly, we have measured the mass of water absorbed as a function of RH, through DVS experiments. *During dissolution*, the excipients are mixed with liquid water. Accordingly, we have also investigated the state of Gelucire 44/14 mixed with known amounts of water, or individual components mixed with known amounts of water. The nature of the phases (crystal, liquid crystal or isotropic solution) that are formed at selected compositions and different temperatures was determined, and their structural parameters were also measured.

components, and their interactions. Thus, in addition to Gelucire 44/14, we also investigated the pure components separately in order to distinguish their specific effects when mixed together. Gelucire 44/14 is composed of polyethylene glycol 33 (PEG 33), PEG mono- and diesters of fatty acids, glycerides and a small amount of glycerol. The most common fatty acid chain in the mixture is laurate. Consequently, we decided to investigate the following chemicals: PEG 33, PEG monolaurate, PEG dilaurate and Trilaurin (triglyceride with laurate chains). By using thermal analysis, microscopy and X-ray diffraction, we investigated the phase behaviour of Gelucire 44/14 and compared it with the phase behaviour of the simple components. In the end, we found that the hydration behaviour of Gelucire 44/14 can be explained by the behaviours of its components.

2. Materials and methods

Gelucire 44/14 (Gattefosse s.a) is produced by the reaction of hydrogenated palm kernel oil and polyethylene glycol, PEG 33 (1500 g/moL). It contains mostly fatty acids of the lauric type (i.e. C12 chains) of which more than 80 % are saturated. The final composition in the Gelucire 44/14 is 72 wt% PEG esters, 20 wt% glycerides, 8 wt% pure PEG and 2% glycerol. The PEG esters are composed by PEG mono- and diesters and the glycerides by mono-, di or triglycerides. Laurate acid chains are the most common type with 40-50 %. The most common chemicals in the Gelucire 44/14 mixture are PEG, PEG mono- and dilaurate (the PEG esters), mono-, di and trilaurates (the glycerides). PEG 33 and trilaurin (triglyceride with laurate chains) were purchased from Sigma. PEG monolaurate and PEG dilaurate were produced by organic synthesis.

PEG ester synthesis

5 g PEG 33 (0,0035 mol) was dissolved in 25 ml ethanol free dichloromethane in a flask. 0,5 ml triethylamin (0,0035 mole) was added to buffer the reaction medium. The flask was put in an ice bath (0 °C). The reaction started by the addition of 0,8 ml lauryl chloride (0,0035 mole). After 2 hours, the mixture contained the products PEG 33, PEG monolaurate and PEG dilaurate. Separation of the products was made by column chromatography on silica gel with a solvent containing dichloromethane:methanol with the proportions 9:1. Finally, the products were washed in cyclohexan to take away excess reactants. The structures of the PEG esters were confirmed by nuclear magnetic resonance, mass- and infrared spectrometry.

Preparation of samples at different humidities

Samples of Gelucire 44/14 were exposed to humidity ratios 0-97 % RH, in order to investigate the humidity effects on the properties of the excipient. The samples were equilibrated in

desiccators containing different saturated salt solutions: silica gel (0%RH), $Mg(NO_3)_2$ (50%RH), $CuCl_2$ (68%RH), NaCl (75%RH), KCl (84%RH) and K_2SO_4 (97%RH).

Preparation of samples with high water contents

To investigate the phase behaviour at high water contents, samples were prepared by mixing directly with water. Samples with weight ratios of component and water from 10/90 to 75/25 were prepared. The component and water were weighed in small glass containers with a scale and sealed with a cap. The samples were mixed by hand and using an ultra sonic water bath. They were left to equilibrate for several weeks before investigation.

Dynamic vapour sorption (DVS)

The dynamic water sorption experiments were made with a DVS thermo-hygro-gravimetric balance under constant nitrogen sweeping and constant temperature (25 °C). The sample (assay sample of about 10 mg) was placed in a glass capsule. It was exposed to a series of relative humidity during a specific time interval at which the absorption of water is measured in weight. The steps are in 10 %RH. The maximum time at each relative humidity is six hours. If equilibrium is reached within this time limit, i.e. the derivative of weight vs. time is <0.02, the measurement automatically moves on to the next humidity.

Small and Wide Angle X-ray Scattering (SWAXS)

To determine the presence of structures in the samples, X-ray diffraction at small and wide angles was used. The SWAXS measurements were performed with a Kratky compact small and wide angle system equipped with a linear collimation system and two position sensitive detectors (Hecus M Braun, Austria). Each detector contains 1024 channels of width 54.0 μm. A monochromator with a nickel filter was used to select the Cu-K_ radiation (λ = 1.541 Å) provided by the generator. The generator, a Seiffert ID-3003 X-ray, was operating at 50 kV and 40 mA. The sample was enclosed in a steel sample holder with mica windows. The distance between the sample and the detector was 279 nm. The measurements were made at room temperature (20°C) unless measurement with temperature increase (20-60°C) was performed.

Thermal Gravimetric Analysis (TGA)

A sample with a mass between 1.5 and 4 mg was deposited in an open 75-_L aluminum crucible. The sample was heated from 20°C to 250°C at a rate of 1°C/min. The analysis was carried out in a nitrogen stream.

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